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EXCIPIENT FOR USE IN DRY POWDER INHALATION PREPARATIONS

The present invention relates to an excipient for use in dry powder inhalation preparations. The invention
5 furthermore relates to dry powder inhalation preparations containing the excipient, to a method for making the excipient and to an excipient made of lactose.

The delivery of active molecules to the lungs can be achieved using metered dose inhalers (MDI), dry powder
10 inhalers (DPI) or nebulisers. In the current market MDI are dominant with DPI a distant second and nebulisers further back. MDI have continued to be successful despite the difficulty of co-ordinating actuation with inhalation and the extensive deposition on the back of the oropharynx due to the
15 high velocity of the droplets.

However, this success has been blighted in recent times by the environmental concerns over chlorofluorocarbons (CFCs), which have been used as propellants. The Montreal
20 protocol in 1989 detailed the need to replace CFC propellants, because of their contribution to ozone depletion. This has resulted in the development of propellants which do not deplete ozone and an increase in activity in the DPI field.

There are a number of DPI products available on the
25 market today, using many different technological approaches for delivering an active component to the lungs. To penetrate into the target areas of the lungs, active molecules must possess an aerodynamic particle size of less than 5µm. This is achieved primarily by micronisation. The particles
30 produced are, however, inherently cohesive/adhesive in nature due to an excess of surface free energy. The surface properties generated in manufacture can lead to adherence to the device and/or the formation of stable agglomerates, both

of which can have a negative influence on the dose reproducibility as they are uncontrollable.

Therefore, traditionally a DPI product consists of the device, the active component and an inert carrier (i.e. excipient) with the purpose to aid flow and encourage dispersion. The active particles adhere to the surface of the carrier, ideally preventing segregation but allowing detachment during inhalation.

The preferred carrier material has always been α -lactose monohydrate. The reasons for this include the fulfillment of the carrier functions by improving flow, the availability of toxicological information and its relatively low price. The manipulation of lactose to balance the requirements of high and constant deposition values and good flow properties has focused primarily on the particle size distribution. However, a number of other techniques have been investigated to improve the performance of lactose as a carrier.

US patent 5,254,330 describes the use of smooth crystals produced by controlled crystallization, which have a rugosity of less than 1.75.

An alternative to α -lactose monohydrate is described in the International patent WO98/50015, which makes use of roller dried anhydrous lactose with a size between 50 and 250 μm and a rugosity between 1.9 and 2.4.

The lactose described in the prior art is in a crystalline form. The particle size is relatively small. It was found that the deposition of these known particles can be further improved.

It is known that decreasing the carrier particle size of a powder mixture, results in an increase in the fine particle fraction. As the particle size is reduced the relationship between the carrier lactose particle and

micronised active component changes. For large carrier particles the active adheres to the surface of the carrier. As carrier size decreases and approaches that of the micronised active component the relationship is more of a weak agglomerate, which can be easily dispersed especially with the modern inhaler devices.

However, as the carrier particle size is decreased, so are the flow properties which affects the distribution of the active component within the mix and the dose reproducibility.

It is the object of the present invention to provide an excipient that can be used as a carrier in dry powder inhalation preparations and that consists of particles large enough to have suitable flow properties and a structure to promote dispersion.

This object is achieved by an excipient for dry powder inhalation preparations comprising granules made of primary carrier material, which granules break up during inhalation in such a manner that they give a concentration of primary carrier material on stage 2 of the twin stage impinger (e.g. by Erweka, UK) determined by the antrone reaction of at least 5%.

Preferably, the concentration of primary carrier material at stage 2 of the twin stage impinger determined by the antrone reaction is at least 10%, more preferably at least 20%.

Such an excipient is obtainable by granulating a primary carrier material in a fluid binding agent, for example in a fluid bed dryer or a shear mixer, and drying the granules thus obtained. The fluid binding agent is preferably an aqueous solution of the primary carrier material. Alternatively, the fluid binding agent is a solvent, in particular ethanol. The properties of the excipient granules

may be varied by choosing the fluid binding agent. A solvent will usually evaporate more quickly thus resulting in weaker granules that lead to a higher percentage at stage 2 of the twin stage impinger.

5 The strength of the granules can be manipulated by varying the process parameters such as the amount of fluid binding agent (granulation fluid).

 Weaker granules have the structure which promotes dispersion of the active component, as they will break down
10 as they pass through an inhaler.

 Drying the granules can be performed in various manners. In general, it was found that the quicker the drying operation, the weaker the granules. Suitable drying means are for example formed by an oven. Especially preferred is drying
15 while the granules are kept in motion, such as in a fluid bed dryer.

 The particle size of the granules that (alone or in combination with some other vehicle) form the excipient lies between 50-1000 μm . Preferably, the particle size of the
20 granules lies between 200-500 μm . The primary particle median geometric size of the granules lies in the range 1-170 μm , preferably in the range 1-15 μm .

 The primary carrier material can be selected from a wide variety of materials which are preferably known to be
25 suitable for DPI, including monosaccharides, such as glucose, fructose, mannose; polyols derived from these monosaccharides, such as sorbitol, mannitol or their monohydrates; disaccharides, such as lactose, maltose, sucrose, polyols derived from these disaccharides, such as
30 lactitol, mannitol, or their monohydrates; oligo or polysaccharides, such as dextrans and starches.

 Preferably the primary carrier material is a crystalline sugar such as glucose, lactose, fructose,

mannitol or sucrose because such sugars are both inactive and safe. Most preferably, lactose is used.

The invention furthermore relates to a dry powder inhalation formulation which contains a pharmacologically active component and an excipient as claimed for delivery of the active component to the lungs.

The active component is for example selected from the group consisting of steroids, bronchodilators, cromoglycate, proteins, peptides and mucolytics, or from the group consisting of hypnotics, sedatives, analgesics, anti-inflammatory agents, anti-histamines, anti-convulsants, muscle relaxants, anti-spasmodics, anti-bacterials, antibiotics, cardiovascular agents, hypoglycaemic agents.

According to a further aspect thereof, the invention relates to a method for producing an excipient as claimed, comprising granulating a primary carrier material in a fluid binding agent and drying the granules thus obtained. The same preferred process parameters apply as indicated above.

The invention in a preferred embodiment thereof relates to lactose granules for use in dry powder inhalation preparations, which granules break down during inhalation in such a manner that they give a concentration of primary carrier material at stage 2 of the twin stage impinger determined by the antrone reaction of at least 5%, preferably at least 10%, more preferably at least 20%. These granules are obtainable by granulating lactose in a lactose solution or a solvent, such as ethanol, and drying the granules thus obtained. The active component is added to the finished granules.

The present invention is further illustrated in the example that follows.

EXAMPLE

To demonstrate the concept of the present invention, granules with a particle size distribution of 200-500 μ m were produced from α -lactose monohydrate (DMV International, the Netherlands) with a particle size distribution of 2-16 μ m. A medium shear mixer (Kenwood) was used to granulate 450 g of lactose using an aqueous lactose solution, water or ethanol as the binding agent, added using a peristaltic pump (LKB). The mass was passed through a 1 mm screen (Erweka) and then dried in a fluid bed dryer (Aeromatic) or tray oven (Heraeus). The 200-500 μ m fraction was prepared by screening with a sieve shaker (Retsch).

The batches were as summarized in Table 1.

Table 1

Batch	Quantity fluid binding agent (w/w)	Lactose concentration in fluid binding agent (w/w)	Mixing time (minutes)	Drying
1	14%	5%	4	Oven
2	14%	5%	4	Fluid bed
3	14%	5%	3	Fluid bed
4	29%	Ethanol (no lactose)	5	Oven
5	20%	5%	4	Fluid bed
6	14%	0%	3	Fluid bed
7	14%	50%	3	Fluid bed

Determining the quantity of lactose on stage 2 by means of the antrone test is performed as follows. The antrone solution is prepared by dissolving 200 mg antrone in 200 g sulphuric acid. 1 ml of sample deposited at stage 2 of the impinger is collected and added to 2 ml of antrone solution. This mixture is allowed to stand for one hour. Subsequently the UV absorbance at 625 nm is determined. The result is given in the following table. The fine particle fraction (FPF) is the active component (e.g. the drug) reaching stage 2 (Table 2), determined as described hereinbelow.

Table 2

% Fine Particle Fraction (%FPF) represented by stage 2

Batch no.	% lactose stage 2	%Fine Particle Fraction (%FPF)
1	1	29.1
2	5	45.8
3	9	51.6
4	24	61.0
5	2	38.6
6	6	48.1
7	8	50.1
Reference (DCL 15)	0	31.2

The granules were blended with the drug sodium cromoglycate (1.8% (w/w)). On completion of the mixing process it was clearly evident that the granules had maintained their initial shape. The formulations were assessed in vitro using the twin stage impinger at 60 l/min which has a cut off diameter of 6.4 μ m, using the Novolizer

Inhaler (Sofotec). The amount of active component on each stage was determined using UV spectroscopy. (Table 3).

Table 3

5	Batch	Inhaler % active component	Stage 1 % active component	Stage 2 % active component (=FPF)	CU (%) (%RSD)
	1	13.5	66.7	29.1	97.7 (6.8)
	2	13.7	51.8	45.8	92.0 (6.6)
	3	8.8	40.3	51.6	96.2 (2.7)
10	4	7.7	23.8	61.0	97.8 (3.4)
	5	16.8	50.2	38.6	94.6 (6.7)
	6	10	43.4	48.1	96.2 (4.4)
15	7	9.5	36.9	50.1	97.7 (1.7)
	Reference	15.8	59.7	31.2	97.2 (4.6)

20 Table 3 shows the in vitro deposition values for the 8 batches of granules (7 according to the invention and 1 reference (DCL 15 from DMV International, the Netherlands)), detailing recovery of active component from the inhaler, stage 1, stage 2 (FPF), content uniformity (CU) and relative
25 standard deviation (%RSD).

Granulation is determined by distribution of liquid over the surface of particles, forming liquid bridges between particles. This is followed by the evaporation of the

liquid resulting in the formation of solid bridges which binds particles together forming granules.

From the results of this experiment it can be derived that decreasing the amount of liquid available for dispersion in granulation, reduces the amount of potential solid bridges producing weaker granules (batch nos. 5 and 2).

Poor dispersion of liquid as a result of shorter mixing times does also produce weaker granules (batch nos. 2 and 3).

Furthermore, it was found that the slower the drying rate the larger the crystals, formed during recrystallisation (batch nos. 1, 2 and 4). Fluid bed drying is faster.

Solids concentration in the liquid has no effect due to the relatively good solubility of lactose (batch nos. 3, 6 and 7).